REMARKS/ARGUMENTS

I. Status of the Claims and Amendments:

Claims 144, 152, 165, 168, 175-177 have been amendment herewith. Claims 144, 147-148, 150-161, 163-168 and 170-192 are pending in the application. Claims 144, 168 and 177 have been amended to recite a molecular switch comprising a mutated progesterone receptor ligand binding domain which is distinct from a naturally occurring ligand binding domain by deletion of up to 54 naturally occurring carboxyl terminal amino acids of the ligand binding domain.

II. Rejections under 35 U.S.C. §112, Written Description

Claims 144, 147, 148, 150-161, 163-168, and 170-192 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. The Examiner contends that "the claims encompass a genus of molecular switches that comprise a mutated progesterone receptor ligand binding domain which is distinct from a naturally occurring ligand binding domain by one or more alterations in from about 1 to about 54 naturally occurring carboxyl terminal amino acids." The Examiner contends that the specification fails to teach lesser deletions or types of mutations such as substitution or insertion to create the molecular switch as claimed and that the claimed genus potentially encompasses a large number of mutated progesterone receptor from various species, while the specification only discloses two deletion mutations of human progesterone receptor that have the molecular switch function as claimed.

Applicant submits that the claims have been amended to recite a mutated progesterone receptor ligand binding domain which is distinct from a naturally occurring ligand binding domain by deletion of up to 54 naturally occurring carboxyl terminal amino acids of the ligand binding domain. To the extent that this rejection is considered to apply to the amended claims, the rejection is respectfully traversed.

With regard to the contention that the specification fails to teach other types of mutation such as substitution or insertion that would also create the molecular switch as claimed, the unexpected result of the instant invention is the functional effect of removing up to 54 amino acids from the carboxyl terminal end of wild-type progesterone receptor ligand binding domain. It has been recognized that written description requirement can be satisfied by functional

description. See, e.g., *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) ("It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement."). Such functional description is sufficient if there is also a structure-function relationship known or disclosed to those of ordinary skill in the art. See, e.g., *In re Wallach*, 378 F.3d 1330, 1335 (Fed. Cir. 2004). Thus, the written description requirement can be met by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, i.e., complete or partial structure, other physical and/or chemical properties, or functional characteristics coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (citing *Guidelines for Examination of Patent Applications under the 35 U.S.C. §112, P 1, "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001)*.

Applicant submits that the instant specification has provided sufficiently detailed and relevant identifying characteristics for the mutated progesterone receptor ligand binding domain disclosed herein. The specification teaches that steroid hormone receptors are modular proteins organized into structurally and functionally defined domains. The ligand binding domain of the native non-mutated steroid hormone receptor is located in the carboxyl-terminal half of the receptor (page 2, lines 17-23). Altering the ligand binding domain by truncating or deleting naturally occurring carboxyl terminal amino acids of the ligand binding domain was found to result in unexpected functional effects, namely reversing the ligand specificity of the receptor so that the receptor is now activated by ligands that are antagonists of the non-mutated hormone receptor. In two working examples, 42 or 54 amino acids were deleted from the carboxyl terminal of the ligand binding domain of the human progesterone receptor (See Figure 4), and ligand-specific transcriptional activities of the mutated receptors were shown in Examples 14-15 and Figures 5-6. Furthermore, the specification provides an example of a method by which the effect of mutations upon the desired function can be readily assessed. In view of such disclosure, one of ordinary skill in the art would readily recognize a structural-function relationship at the carboxyl terminal of the ligand binding domain. Specifically, one of ordinary skill in the art would readily recognize that removal (e.g. by deletion) of up to 54 native amino acids from the carboxyl terminal of the wild-type ligand binding domain would confer activation on the

receptor by ligands that are antagonists of the non-mutated hormone receptor and would be able to readily determine mutations, substitutions and lesser truncations within this area that confer the same effect. One of ordinary skill in the art at the time the application was filed would have readily utilized conventional techniques such as deletion or substitution or other methods to remove naturally occurring amino acids from the carboxyl terminal of the ligand binding domain.

Accordingly, Applicant submits that the instant specification has satisfied the written description requirement for the mutated progesterone receptor ligand binding domain by providing functional characteristics coupled with a correlation between function and structure that is apparent to one of ordinary skill in the art. Furthermore, the specification provides an example of a method by which the effect of mutations upon the desired function can be readily assessed without undue experimentation.

One of ordinary skill in the art would also recognize that such structural-function relationship is not limited to the ligand binding domain of human progesterone receptor. The specification teaches that human and chicken progesterone receptors differ in only a few amino acids (page 32, lines 28-29). At the time the instant application was filed, the sequences for rabbit (Loosfelt et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:9045-9049 (1986)) and murine progesterone receptors (Schott et al., *Biochemistry 30*:7014-7020 (1991)) were also known. An alignment is provided below between the final 60 amino acids of the ligand binding domain of the human, murine (gi|6679295|ref|NP_032855.1), chicken (NP_990593.1 GI:45383982) and rabbit progesterone (gi|130896|sp|P06186|PRGR_RABIT) receptors. Differences from the human receptor sequence are shown in bold.

Human	873	TKLLDNLHDLVKQLHLYCLNTFIQSRALSVEFPEMMSEVIAAQLPKILAGMVKPLLFHKK	933
Chicken	727	TKL**MD**S**M**HDLVKQLHL**F**CLNTFLQSRALSVEFPEMMSEVIAAQLPKILAGMVKPLLFHKK	786
Rabbit	864	TKLLDNLHDLVKQLHLYCLNTFIQSRALSVEFPEMMSEVIAAQLPKILAGMVKPLLFHKK	930
Murine	864	TKLLD**S**LHDLVKQLHLYCLNTFIQSR**T**LAVEFPEMMSEVIAAQLPKILAGMVKPLLFHKK	923

The 54 amino acids at the carboxyl terminal of the ligand binding domain are identical in human and rabbit progesterone receptors, whereas the same 54 amino acid region in human and mouse progesterone receptors differs only in 2 amino acids. Thus, in view of such high sequence

homology among progesterone receptor in various species, one of ordinary skill in the art would reasonably conclude that the structural-function relationship observed at the carboxyl terminal of human progesterone receptor ligand binding domain is equally applicable to progesterone receptor ligand binding domains in other species.

The Examiner further contends that the specification fails to describe progesterone receptors from other species having mutation within this region that have the same molecular switch function. As such, the specification has been asserted to fail to describe a representative number of species by their complete structure or other identifying characteristics. This rejection is respectfully traversed.

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Applicant submits that the instant specification discloses an unexpected functional effect of deleting up to 54 amino acids from the carboxyl terminal end of wild-type progesterone receptor ligand binding domain, and it was known in the art at the time this application was filed that the sequences at this 54 amino acids region were virtually identical in different species as shown above. Thus, in view of the high level of skill and knowledge in the art, Applicant submits that one of ordinary skill in the art would readily recognize a common attribute possessed by the claimed genus in view of the species disclosed herein, namely, deletion or removal of up to 54 amino acids from the carboxyl terminal end of wild-type progesterone receptor ligand binding domain would confer activation on the receptor by ligands that are antagonists of the non-mutated hormone receptor. Accordingly, in view of the high level of skill and knowledge in the art, Applicant submits that the instant specification has provided a representative number of species by disclosing a structural-function relationship at the carboxyl terminal end of progesterone receptor ligand binding domain.

Section 112 requires a determination of whether the specification conveys to one of ordinary skill in the art as of the time the application was filed that an applicant invented what was claimed. *Reiffin v. Microsoft Corp.*, 214 F 3d 1342, 1346, 54 USPQ2d 1915, 1917 (Fed. Cir.

2000). Satisfaction of written description requirement is measured by the understanding of the ordinarily skilled artisan. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). In view of the structural-function relationship observed at the carboxyl terminal of human progesterone receptor ligand binding domain, the virtual identical amino acid sequences of progesterone receptor ligand binding domain in various species, and the high level of skill of an ordinarily artisan in the art of molecular biology, Applicant submits that the instant specification has conveyed to one of ordinary skill in the art as of the time the application was filed that Applicant has invented the claimed subject matter. It should be noted in this context, that the present invention, and especially its application to transgenic animals, was immediately recognized in its field as a particularly valuable technique and has been widely recognized by extensive licensing.

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). The Examiner thus has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Id.* In view of the instant disclosure and the sequence homology discussed above, Applicant submits that the Examiner has failed to present by a preponderance of evidence why a person skilled in the art would not recognize in the present specification a description of the invention defined by the claims.

It may be noted that the patent office has apparently already determined that the written description was met for the claims of related US Patent No. 5,935,934, of which claim 1 is reproduced below:

> 1. A method for regulating expression of a nucleic acid cassette, comprising the steps of:
>
> (a) providing a first nucleic acid cassette which comprises a promoter transcriptionally linked to a mutated receptor protein coding sequence, wherein said mutated receptor protein coding sequence comprises a nucleic acid sequence encoding a mutated receptor protein which regulates the transcription of a molecular switch promoter, and wherein said mutated receptor protein comprises: a DNA binding domain which binds said molecular switch promoter; a mutated steroid hormone receptor superfamily ligand binding domain distinct from a naturally occurring ligand binding domain; a transactivation domain which causes transcription

from said molecular switch promoter when said mutated receptor protein is bound to said molecular switch promoter and to an antagonist for a non-mutated receptor protein;

(b) transcriptionally linking said molecular switch promoter to a nucleic acid encoding a desired protein in a second nucleic acid cassette; and

(c) administering a pharmacologic dose of the first nucleic acid cassette and the second nucleic acid cassette to an animal, wherein said molecular switch promoter is turned on or off by dosing the animal with a pharmacological dose of a ligand which binds to the mutated steroid hormone receptor superfamily ligand binding domain, thereby regulating expression of said second nucleic acid cassette.

In view of the above remarks, Applicant submits that the specification has satisfied the written description requirement. Accordingly, Applicant respectfully requests that the rejection of claims 144, 147, 148, 150-161, 163-168, and 170-192 under 35 U.S.C. §112, first paragraph, be withdrawn.

III. Rejections under 35 U.S.C. §112, Scope of Enablement

Claims 144, 147, 148, 150-161, 163-168, and 170-192 are rejected under 35 U.S.C. §112, first paragraph, for failing to provide sufficient enablement commensurate in scope with the claims. The Examiner contends that the specification does not reasonably provide enablement for utilizing any transgenic animal or long term expression in any animal, and/or any mutated steroid hormone receptor that is capable of binding ligand that is an antagonist of the natural occurring receptor. Applicant respectfully traverses.

With regard to the contention that the specification was not enabling for regulating gene expression using any mutated steroid hormone receptor, Applicant submits that in the interests of advancing prosecution, the claims have been amended in prior response to recite the ligand binding domain is a mutated progesterone receptor ligand binding domain. Hence, the claims as amended do not read on using any mutated steroid hormone receptor.

With regard to the contention that the specification was not enabling for utilizing any transgenic animal or long term expression in any animal, apparently the Examiner is arguing that the claimed method is enabling only to the extend that the molecular switch is expressed in the animal as stated in previous office action. Applicant submits that the claims have been amended to recite the molecular switch is expressed in the animal. The claims also recite a target gene

controlled by specific promoter would be expressed as a consequence of ligand administration in an animal expressing a molecular switch that has a DNA binding domain specific for the promoter to the target gene. Hence, according to the Examiner's reasoning, the claims as amended are fully enabled for utilizing any transgenic animal.

The Examiner further contends that the specification fails to teach whether deletion of 1-54 amino acids from the carboxyl terminal of the ligand binding domain of progesterone receptor of other species would also result in the molecular switch as claimed. Applicant respectfully traverses.

The scope of the required enablement varies inversely with the degree of predictability involved. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. As discussed above, it was known at the time of filing that the sequence of progesterone receptor is highly homologous in various species. The carboxyl terminal 54 amino acids of the progesterone receptor ligand binding domain are virtually identical in human, mouse, rabbit and chicken. In view of such high sequence homology, Applicant submits that one skilled in the art would readily anticipate that the functional effect of deleting or removing the carboxyl terminal 54 amino acids observed herein can be readily extrapolated to other species.

The present inventors found that carboxyl terminal deletion to the progesterone receptor ligand binding domain actually abolished progesterone binding. The inventors also found that, based on the fact that deletion of as much as 54 carboxyl terminal amino acids did not affect antiprogestin binding but in fact allowed antiprogestins to have agonistic effect, that the region responsible for antiprogestin binding was necessarily upstream of the mutated region. Using these concrete endpoints, it would be straightforward in accordance with the high level of skill in the art to delete or remove the carboxyl terminal amino acids that destroyed progesterone binding while retaining the antiprogestin effect. Given the high level of skill in the art, routine

experimentation would be sufficient to make further useful mutants given the discovery as disclosed.

Furthermore, it is the Examiner's burden to clearly establish a *prima facie* case of lack of enablement by presenting sound scientific reason supported by references that establish a conclusion that the specification is not enabling. Applicant submits that the Examiner has failed to provide such scientific evidence in view of the facts known to one of ordinary skill in the art at the time of filing.

In view of the above remarks, Applicant submits that the specification has provided sufficient enablement commensurate in scope with the claims. Accordingly, Applicant respectfully requests that the rejection of claims 144, 147, 148, 150-161, 163-168, and 170-192 under 35 U.S.C. §112, first paragraph, be withdrawn.

The Commissioner is authorized to charge any additional fees incurred in this application or credit any overpayment to Deposit Account No. 50-1922. Should the Examiner have any questions, please do not hesitate to call Applicants' attorney at 832-446-2421.

Respectfully submitted,

By _____

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